

# Comparison of airway pressure release ventilation to conventional mechanical ventilation in the early management of smoke inhalation injury in swine\*

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**Objective:** The role of airway pressure release ventilation in the management of early smoke inhalation injury has not been studied. We compared the effects of airway pressure release ventilation and conventional mechanical ventilation on oxygenation in a porcine model of acute respiratory distress syndrome induced by wood smoke inhalation.

**Design:** Prospective animal study.

**Setting:** Government laboratory animal intensive care unit.

**Patients:** Thirty-three Yorkshire pigs.

**Interventions:** Smoke inhalation injury.

**Measurements and Main Results:** Anesthetized female Yorkshire pigs ( $n = 33$ ) inhaled room-temperature pine-bark smoke. Before injury, the pigs were randomized to receive conventional mechanical ventilation ( $n = 15$ ) or airway pressure release ventilation ( $n = 12$ ) for 48 hrs after smoke inhalation. As acute respiratory distress syndrome developed ( $\text{PaO}_2/\text{FiO}_2$  ratio  $< 200$ ), plateau pressures were limited to  $< 35$  cm  $\text{H}_2\text{O}$ . Six uninjured pigs received conventional mechanical ventilation for 48 hrs and served as time controls. Changes in  $\text{PaO}_2/\text{FiO}_2$  ratio, tidal volume, respiratory rate, mean airway pressure, plateau pressure, and hemodynamic variables were recorded. Survival was assessed using Kaplan-Meier analysis.  $\text{PaO}_2/\text{FiO}_2$  ratio was lower in airway pressure release

ventilation vs. conventional mechanical ventilation pigs at 12, 18, and 24 hrs ( $p < .05$ ) but not at 48 hrs. Tidal volumes were lower in conventional mechanical ventilation animals between 30 and 48 hrs post injury ( $p < .05$ ). Respiratory rates were lower in airway pressure release ventilation at 24, 42, and 48 hrs ( $p < .05$ ). Mean airway pressures were higher in airway pressure release ventilation animals between 6 and 48 hrs ( $p < .05$ ). There was no difference in plateau pressures, hemodynamic variables, or survival between conventional mechanical ventilation and airway pressure release ventilation pigs.

**Conclusions:** In this model of acute respiratory distress syndrome caused by severe smoke inhalation in swine, airway pressure release ventilation-treated animals developed acute respiratory distress syndrome faster than conventional mechanical ventilation-treated animals, showing a lower  $\text{PaO}_2/\text{FiO}_2$  ratio at 12, 18, and 24 hrs after injury. At other time points,  $\text{PaO}_2/\text{FiO}_2$  ratio was not different between conventional mechanical ventilation and airway pressure release ventilation. (Crit Care Med 2011; 39:2314–2321)

**KEY WORDS:** acute respiratory distress syndrome; mechanical ventilation; smoke inhalation injury; swine

Inhalation injury complicates approximately 10% of admissions to burn centers in the United States (1). Presence of inhalation injury

independently increases mortality over that predicted by age and burn size alone by up to 20% in the absence of pneumonia, and by up to 60% if pneumonia also occurs (2). Smoke inhalation injury encompasses: 1) injury to the upper airway; 2) injury to the lower airways and pulmonary parenchyma; and 3) systemic toxicity from inhalation of toxic gases (3). While upper airway injury and systemic toxicity are both critical in the immediate management of inhalation injury, subglottic injury (i.e., injury to the lower airways and pulmonary parenchyma) contributes significantly to challenges in management during the ensuing days and weeks.

Subglottic inhalation injury is primarily a chemical injury induced by the products of combustion (4). This injury is characterized by bronchospasm, mucosal hyperemia, increased microvascular permeability, and the formation of obstruc-

tive casts secondary to the influx of inflammatory cells, exfoliated bronchial epithelial cells, and mucus (5, 6). Small airway obstruction promotes further lung injury through barotrauma, atelectasis (7), and pneumonia (8). Smoke inhalation also disrupts alveolar function by increasing endothelial permeability and deactivating pulmonary surfactant and ciliary function (9, 10).

Acute respiratory distress syndrome (ARDS) is a complication of smoke inhalation injury, with an incidence as high as 54% in mechanically ventilated burn patients (11). ARDS may result directly from smoke toxicity or indirectly from inflammatory mediators associated with infection or the burn wound itself (12). Low tidal volume (TV) ventilation has been shown to reduce mortality in ARDS in multiple trials by reducing barotrauma and volutrauma (13–17). Several “lung-protective” modes of ventilation have

## \*See also p. 2376.

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been described in smoke inhalation injury, but controversy still exists as to which ventilation mode provides the greatest benefit (18–23).

Airway pressure release ventilation (APRV) is a mode of ventilation that optimizes mean airway pressure (Paw), by maintaining a continuous positive airway pressure interrupted by time-cycled short releases of pressure to facilitate ventilation. It has been advocated in the management of ARDS (20). One of the theoretical advantages of APRV is that it allows for spontaneous ventilation throughout the entire ventilation cycle, especially during high lung inflation, which may enhance and maintain alveolar recruitment. Spontaneous breathing during APRV has been associated with improved dependent lung expansion and thereby with improved ventilation-perfusion matching (24, 25). APRV has been associated with improved oxygenation, lower end-inhalation pressures, and less sedation, although it has yet to demonstrate a mortality benefit when compared to conventional mechanical ventilation (CMV) (26–29). There have been no publications to date evaluating the use of APRV in smoke inhalation injury. We hypothesized that APRV would improve PaO<sub>2</sub>/Fio<sub>2</sub> ratio (PFR) when compared to CMV during the first 48 hrs after severe smoke inhalation in a porcine model.

## MATERIALS AND METHODS

This study was approved by the U.S. Army Institute of Surgical Research Animal Care and Use Committee. It was conducted in compliance with the Animal Welfare Act and the implementing Animal Welfare Regulations and in accordance with the principles of the Guide for the Care and Use of Laboratory Animals.

**Animal Preparation.** Female, nonpregnant, Yorkshire pigs (n = 33) were anesthetized with tiletamine/zolazepam (4–6 mg/kg intramuscular) followed by isoflurane (1%–3%). Endotracheal intubation was performed with a 10-F endotracheal tube via direct laryngoscopy. Inhalation anesthesia was transitioned to total intravenous anesthesia via continuous-rate infusion of ketamine hydrochloride (20–30 mg/kg/hr), midazolam hydrochloride (1.0–1.5 mg/kg/hr), and propofol (50–100 µg/kg/min). Animals were ventilated with the Dräger Evita XL ventilator (Dräger Medical, Lübeck, Germany) in a volume-controlled mode with a baseline setting of TV 10 mL/kg, a positive-end expiratory pressure (PEEP) 5 cm H<sub>2</sub>O, an inspiratory/expiratory ratio of 1:3, and Fio<sub>2</sub> 21%. Respiratory rate was adjusted to maintain a

APRV Initial Settings		
Protocol goal keep Pplat < 35 cmH <sub>2</sub> O		
P High = 2 cmH <sub>2</sub> O above current P <sub>aw</sub>		
P Low = 0		
T High = 5 s		
T Low = 0.6 s		
FiO <sub>2</sub> = 21%		

Adjusting for Hypercarbia	Adjusting for Hypoxemia	Adjusting for Hypocarbida
Goal: PaCO <sub>2</sub> < 60, pH > 7.2	Goal: PaO <sub>2</sub> > 70, SpO <sub>2</sub> > 92%	Goal: PaCO <sub>2</sub> > 30, pH < 7.5
1. Decrease sedation to allow spontaneous breathing	1. Increase P High by 2	1. If PaO <sub>2</sub> > 100, decrease P High by 2
2. Increase P High by 2	2. If PCO <sub>2</sub> < 50, then decrease T Low by 0.1	2. Decrease T Low by 0.1
3. Increase T Low by 0.1 s	3. Repeat 1 and 2 until P High 40; T Low 0.4 s	3. Repeat 1 and 2 until P High 20 and T Low 0.4 s
4. Repeat 2 and 3 until P High 40; T Low 1.2 s	4. Titrate FiO <sub>2</sub> to lowest possible setting to maintain oxygenation goals	
5. Decrease T High to 3.5 s		

Figure 1. Airway pressure release ventilation (APRV) algorithm. Pplat, plateau pressure; Paw, mean airway pressure.

Paco<sub>2</sub> between 35 and 45 mm Hg. Arterial, venous, pulmonary artery, and urinary bladder catheters were placed, and a tracheostomy was performed.

**Wood Smoke Inhalation Injury.** Upon completion of the above procedures, baseline values were obtained and the animals were transported to a procedure room for administration of smoke as previously described (30). Briefly, the smoke apparatus consists of a combustion chamber, a mixing box, a hand-operated piston, and modified ventilator tubing. The wood chips are burned in the combustion chamber, after which the smoke is passed into the mixing box. There, it is cooled to avoid thermal injury to the animals and mixed with 100% oxygen. Next the smoke is delivered to the animals through the tracheostomy using a hand-operated piston. TV per smoke breath was set at 30 mL/kg. This large TV constitutes an integral part of our smoke inhalation injury procedure. Our goal for smoke delivery was to achieve an arterial carboxyhemoglobin (COHb) level of 80% determined via blood gas analysis (Cobas b221, Roche Diagnostics, Indianapolis, IN) at the end of smoke delivery, since in our experience this is likely to lead to acute lung injury/ARDS in the majority of injured animals. Because COHb was not continuously measurable in real time, we used smoke volume as a surrogate target. We previously determined that administration of 28–30 L of smoke was likely to achieve our COHb goal. However, smoke injury was terminated before that point if the pig developed hemodynamic instability, manifested by hypotension, or desaturation during the injury.

After injury, pigs were transported to the animal intensive care unit, where they remained under round-the-clock clinical monitoring for 48 hrs. Analgesia was provided with buprenorphine (0.05 mg/kg intramuscular) every 6 hrs throughout the study. Suctioning was performed as needed. Fiberoptic bronchoscopy was performed at 2, 6, 12, and 24 hrs after injury. If endotracheal tube or tracheo-

bronchial obstruction was observed during bronchoscopy, airway casts and debris were removed. Pigs also received a maintenance intravenous infusion of lactated Ringer's solution at a rate sufficient to produce a urine output of 0.5 to 1 mL/kg/hr. Injured pigs were included in this study if they developed acute lung injury, defined as a PaO<sub>2</sub>/Fio<sub>2</sub> ratio <300, at any time during the experiment. Pigs were excluded if they failed to achieve acute lung injury.

**Mechanical Ventilation Protocol.** Before injury, pigs were randomized to receive either CMV (n = 15) or APRV (n = 12). For 2 hrs after injury, a Fio<sub>2</sub> of 100% was used to accelerate carbon monoxide clearance. Other ventilator settings continued as at baseline with a TV of 10 mL/kg, respiratory rate of 12 breaths/min, and PEEP of 5 cm H<sub>2</sub>O. After 2 hrs, Fio<sub>2</sub> was weaned to achieve an arterial oxygen saturation of >92%. During the first 6 hrs after injury, pigs were either continued on CMV or placed on APRV (Figs. 1 and 2). The CMV algorithm involved PEEP adjustments according to the original ARDS Network titration table (14). A goal for maintenance of plateau pressure (Pplat) <35 cm H<sub>2</sub>O was used for both CMV and APRV arms. Six uninjured pigs were maintained on CMV at TV of 10 mL/kg, PEEP of 5 cm H<sub>2</sub>O, and Fio<sub>2</sub> of 21%, and served as time controls. Pigs in all three groups received humidification via a Fisher-Paykel Healthcare MR850JHU humidifier (Auckland, NZ).

**Measurements.** The following variables were measured: body weight, number of smoke breaths received, volume of smoke received, peak COHb levels after completion of smoke injury, heart rate, mean arterial pressure, cardiac output, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, pH, Paco<sub>2</sub>, PaO<sub>2</sub>, TV, respiratory rate, minute ventilation, peak inspiratory pressure, Pplat, Paw, and PFR. These variables were recorded at baseline (before injury), 30 mins, 60 mins, 2 hrs, 6 hrs, and every 6 hrs thereafter for 48 hrs. Oxygen saturation of peripheral arterial

blood was continuously monitored via pulse oximetry. After 48 hrs, all animals were euthanized with a euthanasia solution (Fatal-Plus, Med-Vet International, Mettawa, IL) in accordance with the American Veterinary Medical Association Guidelines on Euthanasia, June 2007.

**Histology.** Following euthanasia 48 hrs after injury (or earlier for nonsurvivors), sections were taken from the right and left apical and caudal lobes, fixed in neutral-buffered 10% formalin for 24 hrs, trimmed, embedded in paraffin, sectioned at 4  $\mu$ m, and stained with hematoxylin and eosin. Histologic grading of injury was performed as previously described by a veterinary pathologist using the following scores (30):

- 1) Bronchial injury. Degeneration/necrosis within small bronchi (0 = normal; 1 = cilia loss; 2 = thinning of apical epithelium only; 3 = <50% segmental/focal ulceration of epithelium; 4 = >50% ulceration of epithelium).
- 2) Alveolar inflammation. Degeneration and inflammation of alveolar septae (0 = normal; 1 = minimal or mild thickening of alveolar septae, relatively few inflammatory cells; 2 = mild to moderate thickening of alveolar septae, increased number of inflammatory cells; 3 = moderate thickening of alveolar septae, relatively large number of inflammatory cells, <50% hyaline membrane formation; 4 = necrosis of alveolar septae, >50% hyaline membrane formation).
- 3) Alveolar hemorrhage/edema. Relative amount of alveoli containing hemorrhage and edema (0 = Normal; 1 = <25% alveoli

contain hemorrhage or edema; 2 = 25%–50% alveoli contain hemorrhage or edema; 3 = 50%–75% alveoli contain hemorrhage or edema; 4 = >75% alveoli contain hemorrhage or edema).

**Statistical Analysis.** All values expressed are means  $\pm$  SEM. Statistical analyses were performed using SAS 9.1 software. These included two-way analysis of variance with repeated measures and Tukey-Kramer adjustment for multiple comparisons, two-tailed Student's *t* test, or Wilcoxon two-sample test. Survival was evaluated using Kaplan-Meier analysis. Ordinal data, specifically, the histologic score, were analyzed using the Kruskal-Wallis test and *post hoc* Wilcoxon Two-Sample test, with Bonferroni correction for multiple comparisons. Significance was accepted at *p* < .05. Non-normally distributed data were log transformed before analysis.

RESULTS

Out of the 33 experiments performed, 30 pigs were included in the study (CMV = 15, APRV = 9, time controls = 6). Three were excluded in the APRV group because their peak COHb levels were below the study target of 80% COHb and they failed to develop acute lung injury at any time during the experiment. These three animals also did not have bronchoscopic or histologic evidence of significant smoke inhalation injury. All other animals achieved the 80% end-

injury COHb target except one in the CMV group. However, that animal did develop ARDS at end of the study and thus was considered for analysis.

Body weight, smoke dose, and postintubation peak carbon monoxide levels did not differ between the APRV and the CMV groups, indicating consistent injury levels between the groups (Table 1).

A total of eight pigs died before 48 hrs (six in the CMV group and two in the APRV group). Causes of death were acute desaturation (two in the APRV group and four in the CMV group) as well as pneumothorax (two animals in the CMV group; diagnosis confirmed radiologically). Four of the six deaths in the CMV group occurred when bronchoscopy was not available at night. In the CMV group, at 24 hrs mortality was 13%, and at 48 hrs mortality was 40%. In the APRV group, mortality was 22% at both 24 and 48 hrs. As shown by Kaplan-Meier analysis (Fig. 3), there was no significant difference in survival rate between the groups (*p* = .19 by log-rank test).

PFR declined more quickly in APRV than in CMV animals. PFR was lower in both CMV and APRV animals as compared to controls at 18 hrs and all time points thereafter (Fig. 4). PFR in the APRV group was also lower than that of controls at 12 hrs. PFR was lower in the APRV group compared to CMV at 12, 18, and 24 hrs (Fig. 4). By the end of the 48-hr study, the differences in PFR between surviving APRV and CMV pigs had disappeared (Table 1).

Hemodynamic and blood gas data are provided in Table 2. Heart rate was lower and higher in the APRV group at 30 and 36 hrs respectively (Table 2). There were no statistically significant differences in mean arterial pressure. Mean pulmonary arterial pressure was lower in the CMV group at 18, 24, and 30 hrs. Pulmonary capillary wedge pressure was lower in the CMV group at 12, 18, and 36 hrs, and pH was lower in the CMV group at 42 hrs. Other variables did not change after injury (Table 2).

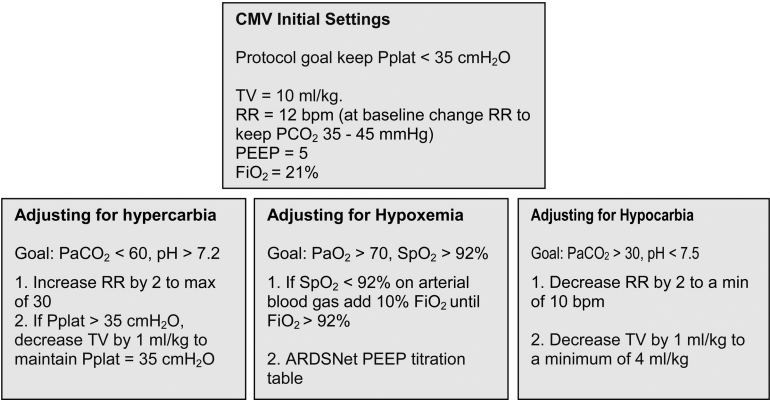


Figure 2. Conventional mechanical ventilation (CMV) algorithm. TV, tidal volume; RR, respiratory rate; PEEP, positive end-expiratory pressure; Pplat; plateau pressure.

Table 1. Inhalation injury data

Group	Weight (kg)	Smoke Breaths	Smoke (L)	Peak Carboxyhemoglobin (%)	PaO <sub>2</sub> /Fio <sub>2</sub> Ratio at 24 hrs	PaO <sub>2</sub> /Fio <sub>2</sub> Ratio 48 hrs	Mean Survival Time
Conventional mechanical ventilation	42.8 $\pm$ 9	24 $\pm$ 1	30.4 $\pm$ 2	84.2 $\pm$ 2	2.46 $\pm$ 0.3	0.92 $\pm$ 0.24	38.3 $\pm$ 3.8
Airway pressure release ventilation	42.5 $\pm$ 1	23.2 $\pm$ 1	29.9 $\pm$ 2	87.3 $\pm$ 2	1.18 $\pm$ 0.30	1.59 $\pm$ 0.57	42 $\pm$ 4
<i>p</i>	.56	.72	.88	.67	.02	.31	.42

Values are means  $\pm$  SEM. Significance by two-tailed Student's *t* test or Wilcoxon two-sample test.



Ventilator data are provided in Table 3. TV was consistently lower in the CMV group after 30 hrs post injury. Respiratory rate was higher in the CMV group at hours 24, 42, and 48. Minute ventilation was lower in APRV at 24 hrs. Peak in-

spiratory pressure and Pplat were not different. However, Paw was sustained at higher levels in the APRV group at 6 hrs and all subsequent time points (Table 3).

Airway cast formation was a prominent and consistent gross observation in

all injured animals. Bronchial and alveolar histologic findings are shown in Figure 5. Control animals had multifocal loss of cilia (Fig. 5A) whereas both the APRV and CMV injury groups featured diffuse loss of cilia, multifocal ulceration, fibrin deposition, hemorrhage, and intraluminal debris (Fig. 5B and C). We also identified widespread multifocal thickening and disruption of alveolar septae, edema, hemorrhage, and fibrinocellular debris in the APRV and CMV groups (Fig. 5E and F). Septal thickening, disruption, and alveolar edema were also sporadically present in the controls (Fig. 5D).

The scoring results are presented in Table 4. Specifically, bronchial injury scores were significantly higher in the APRV and CMV groups than in the control group, but not different between the two injury groups. Both side-specific and apical vs. basal scores for alveolar inflammation and alveolar hemorrhage/edema were numerically higher in the injury groups compared to controls, but statistical significance was not reached. The cumulative bronchial injury scores were identical in APRV and CMV groups and higher than in the controls (Table 4).

## DISCUSSION

We compared effects of APRV and CMV on PFR during management of smoke inhalation injury in swine. The major finding of this study is that APRV, an open-lung ventilation approach, did not improve PFR compared to CMV. This occurred despite higher Paw in the APRV group. This is a severe model of inhalation injury, resulting in a significant early ARDS rate and significant early

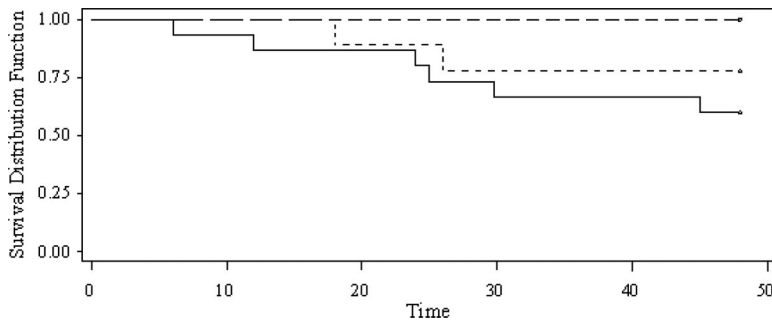


Figure 3. Kaplan-Meier survival curves. Kaplan-Meier survival curves. *Longer dash lines* denote controls, *short dashed line* is conventional mechanical ventilation group, and *bold line* denotes airway pressure release ventilation group. Differences in survival rates are not significant between groups by log-rank test ( $p = .19$ ).

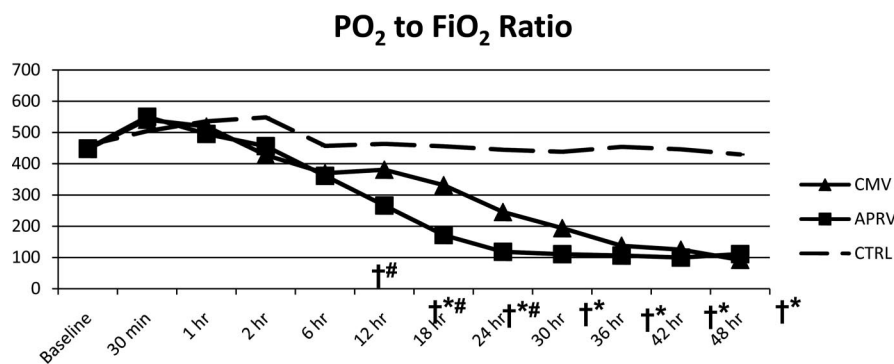


Figure 4. Changes in  $\text{PaO}_2/\text{FiO}_2$  ratio over time. Solid line with *squares* is the airway pressure release ventilation (APRV) group, solid line with *triangles* is conventional mechanical ventilation (CMV) group, and *dashed line* denotes controls (CTRL). Values are means  $\pm$  standard error. Daggers indicate significant differences between APRV and CTRL. Asterisks indicate significant difference between CMV and controls. Pound signs indicate significant difference between CMV and APRV. Statistical analysis was done by two-way analysis of variance with repeated measures and Tukey-Kramer adjustment for multiple comparisons. Significance at  $p < .05$ .

Table 2. Hemodynamic and blood gas data

Variable	Group	Baseline	30 mins	60 mins	2 hrs	6 hrs	12 hrs	18 hrs	24 hrs	30 hrs	36 hrs	42 hrs	48 hrs
Heart rate (beats per minute)	CMV	91 $\pm$ 4	149 $\pm$ 8	150 $\pm$ 7	144 $\pm$ 7	140 $\pm$ 8	115 $\pm$ 7	107 $\pm$ 6	100 $\pm$ 7	109 $\pm$ 5	92 $\pm$ 6	101 $\pm$ 6	102 $\pm$ 7
	APRV	96 $\pm$ 10	151 $\pm$ 14	140 $\pm$ 15	132 $\pm$ 12	134 $\pm$ 12	101 $\pm$ 7	107 $\pm$ 9	111 $\pm$ 7	93 $\pm$ 5 <sup>a</sup>	112 $\pm$ 6 <sup>a</sup>	109 $\pm$ 8	112 $\pm$ 8
Mean arterial pressure (mm Hg)	CMV	110 $\pm$ 8	109 $\pm$ 5	102 $\pm$ 6	96 $\pm$ 5	85 $\pm$ 5	76 $\pm$ 4	69 $\pm$ 4	71 $\pm$ 6	76 $\pm$ 5	85 $\pm$ 5	84 $\pm$ 3	92 $\pm$ 6
	APRV	110 $\pm$ 6	100 $\pm$ 9	95 $\pm$ 8	98 $\pm$ 7	81 $\pm$ 5	82 $\pm$ 6	76 $\pm$ 5	80 $\pm$ 7	74 $\pm$ 6	81 $\pm$ 6	75 $\pm$ 4	80 $\pm$ 4
Cardiac output (L/min)	CMV	5.4 $\pm$ 0	6.3 $\pm$ 0	6.0 $\pm$ 0	5.2 $\pm$ 0	3.8 $\pm$ 0	3.3 $\pm$ 0	3.0 $\pm$ 0	3.2 $\pm$ 0	3.8 $\pm$ 0	3.8 $\pm$ 0	4.0 $\pm$ 0	4.3 $\pm$ 0
	APRV	5.0 $\pm$ 0	5.2 $\pm$ 0	5.2 $\pm$ 0	4.3 $\pm$ 0	3.4 $\pm$ 0	2.9 $\pm$ 0	2.9 $\pm$ 0	3.8 $\pm$ 0	3.8 $\pm$ 0	4.3 $\pm$ 0	3.6 $\pm$ 0	4.5 $\pm$ 1
Mean pulmonary artery pressure (mm Hg)	CMV	20 $\pm$ 1	19 $\pm$ 1	19 $\pm$ 1	20 $\pm$ 1	27 $\pm$ 1	25 $\pm$ 2	28 $\pm$ 1	28 $\pm$ 1	29 $\pm$ 1	31 $\pm$ 2	34 $\pm$ 2	33 $\pm$ 1
	APRV	21 $\pm$ 2	21 $\pm$ 3	22 $\pm$ 3	20 $\pm$ 3	26 $\pm$ 2	30 $\pm$ 3	34 $\pm$ 2 <sup>a</sup>	35 $\pm$ 1 <sup>a</sup>	34 $\pm$ 1 <sup>a</sup>	36 $\pm$ 2	33 $\pm$ 3	42 $\pm$ 8
Pulmonary capillary wedge pressure (mm Hg)	CMV	9 $\pm$ 1	9 $\pm$ 1	9 $\pm$ 1	8 $\pm$ 1	8 $\pm$ 1	9 $\pm$ 1	9 $\pm$ 1	11 $\pm$ 1	9 $\pm$ 1	9 $\pm$ 1	10 $\pm$ 1	11 $\pm$ 1
	APRV	9 $\pm$ 1	8 $\pm$ 1	8 $\pm$ 1	10 $\pm$ 2	11 $\pm$ 1	12 $\pm$ 1 <sup>a</sup>	14 $\pm$ 3 <sup>a</sup>	14 $\pm$ 3	15 $\pm$ 4	13 $\pm$ 2 <sup>a</sup>	13 $\pm$ 2	10 $\pm$ 1
pH	CMV	7.45 $\pm$ 0	7.35 $\pm$ 0	7.36 $\pm$ 0	7.38 $\pm$ 0	7.41 $\pm$ 0	7.42 $\pm$ 0	7.38 $\pm$ 0	7.36 $\pm$ 0	7.38 $\pm$ 0	7.41 $\pm$ 0	7.39 $\pm$ 0	7.38 $\pm$ 0
	APRV	7.44 $\pm$ 0	7.39 $\pm$ 0	7.41 $\pm$ 0	7.40 $\pm$ 0	7.44 $\pm$ 0	7.42 $\pm$ 0	7.35 $\pm$ 0	7.32 $\pm$ 0	7.39 $\pm$ 0	7.39 $\pm$ 0	7.50 $\pm$ 0 <sup>a</sup>	7.46 $\pm$ 0
Paco <sub>2</sub> (mm Hg)	CMV	42 $\pm$ 1	47 $\pm$ 1	47 $\pm$ 1	47 $\pm$ 1	47 $\pm$ 2	42 $\pm$ 2	45 $\pm$ 2	50 $\pm$ 3	50 $\pm$ 4	49 $\pm$ 4	52 $\pm$ 3	53 $\pm$ 3
	APRV	42 $\pm$ 1	40 $\pm$ 3 <sup>a</sup>	39 $\pm$ 4 <sup>a</sup>	42 $\pm$ 6	42 $\pm$ 3	43 $\pm$ 4	52 $\pm$ 5	55 $\pm$ 3	50 $\pm$ 3	54 $\pm$ 6	44 $\pm$ 5	44 $\pm$ 4
PaO <sub>2</sub> (mm Hg)	CMV	94 $\pm$ 2	541 $\pm$ 1	519 $\pm$ 2	428 $\pm$ 3	112 $\pm$ 1	114 $\pm$ 1	105 $\pm$ 2	87 $\pm$ 7	88 $\pm$ 6	78 $\pm$ 4	88 $\pm$ 13	73 $\pm$ 8
	APRV	94 $\pm$ 1	550 $\pm$ 2	495 $\pm$ 4	456 $\pm$ 6	140 $\pm$ 2	100 $\pm$ 1	82 $\pm$ 5	75 $\pm$ 6	83 $\pm$ 13	81 $\pm$ 16	78 $\pm$ 10	77 $\pm$ 10

CMV, conventional mechanical ventilation; APRV, airway pressure release ventilation.

<sup>a</sup>indicates  $p < .05$  determined by two-way analysis of variance with repeated measures.

Hemodynamic and blood gas data recorded at baseline and respective time points of the experiment. Values are means  $\pm$  SEM.

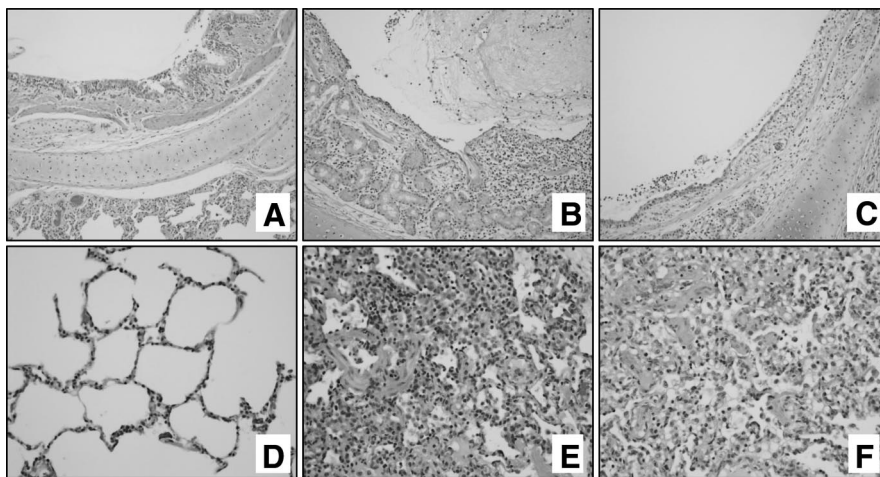
Table 3. Ventilatory data

Ventilatory Parameter	Group	Baseline	30 mins	60 mins	2 hrs	6 hrs	12 hrs	18 hrs	24 hrs	30 hrs	36 hrs	42 hrs	48 hrs
Tidal volume (mL)	CMV	427 ± 10	426 ± 11	425 ± 10	403 ± 14	380 ± 15	372 ± 17	350 ± 19	343 ± 18	343 ± 24	304 ± 25	268 ± 14	261 ± 15
	APRV	431 ± 18	534 ± 79	525 ± 74	494 ± 76	411 ± 36	407 ± 24	396 ± 36	390 ± 38	452 ± 56 <sup>a</sup>	498 ± 59 <sup>a</sup>	535 ± 73 <sup>a</sup>	518 ± 65 <sup>a</sup>
Tidal volume (mL/kg)	CMV	10 ± 0	10 ± 0	10 ± 0	9 ± 0	9 ± 0	9 ± 0	8 ± 1	8 ± 1	8 ± 1	7 ± 1	6 ± 0	6 ± 0
	APRV	10 ± 0	12 ± 1 <sup>a</sup>	12 ± 1	11 ± 1	10 ± 1	10 ± 1	9 ± 1	9 ± 1	11 ± 1 <sup>a</sup>	12 ± 1 <sup>a</sup>	13 ± 1 <sup>a</sup>	12 ± 1 <sup>a</sup>
Respiratory rate (rate per minute)	CMV	12 ± 0	12 ± 0	12 ± 0	12 ± 0	14 ± 1	15 ± 1	17 ± 2	19 ± 2	21 ± 2	24 ± 2	27 ± 1	28 ± 1
	APRV	12 ± 0	12 ± 0	14 ± 1	13 ± 0	13 ± 0	17 ± 4	14 ± 1	14 ± 1 <sup>a</sup>	19 ± 4	22 ± 4	16 ± 3 <sup>a</sup>	16 ± 3 <sup>a</sup>
Minute ventilation (L/min)	CMV	4.9 ± 0.1	5.5 ± 0.3	5.2 ± 0.3	4.9 ± 0.1	5.1 ± 0.2	5.1 ± 0.2	5.5 ± 0.3	6.0 ± 0.3	6.7 ± 0.3	6.7 ± 0.3	6.9 ± 0.4	7.0 ± 0.3
	APRV	4.6 ± 0.2	6.1 ± 0.9	8.1 ± 2.0	6.3 ± 1.2	5.1 ± 0.3	5.3 ± 0.4	5.0 ± 0.2	4.8 ± 0.3 <sup>a</sup>	6.2 ± 0.7	7.4 ± 0.9	6.5 ± 0.5	6.3 ± 0.5
Peak inspiratory pressure (cm H <sub>2</sub> O)	CMV	16 ± 0	17 ± 1	20 ± 1	23 ± 2	28 ± 3	29 ± 3	33 ± 2	31 ± 2	36 ± 2	40 ± 4	44 ± 4	41 ± 3
	APRV	16 ± 0	19 ± 2	22 ± 2	26 ± 2	24 ± 2	26 ± 2	31 ± 2	33 ± 3	34 ± 2	37 ± 2	35 ± 3	35 ± 2
Plateau pressure (cm H <sub>2</sub> O)	CMV	15 ± 0	16 ± 1	18 ± 1	21 ± 1	26 ± 2	26 ± 2	27 ± 1	27 ± 1	32 ± 1	35 ± 3	37 ± 3	34 ± 2
	APRV	15 ± 1	18 ± 2	21 ± 2	23 ± 2	23 ± 2	25 ± 2	31 ± 2	31 ± 3	32 ± 2	35 ± 2	33 ± 3	31 ± 2
Mean airway pressure (cm H <sub>2</sub> O)	CMV	7 ± 0	8 ± 0	8 ± 0	8 ± 0	9 ± 0	9 ± 0	11 ± 1	12 ± 1	13 ± 1	14 ± 1	17 ± 1	16 ± 1
	APRV	8 ± 1	8 ± 1	10 ± 1	12 ± 1	19 ± 2 <sup>a</sup>	22 ± 2 <sup>a</sup>	24 ± 1 <sup>a</sup>	25 ± 2 <sup>a</sup>	26 ± 2 <sup>a</sup>	28 ± 2 <sup>a</sup>	28 ± 3 <sup>a</sup>	27 ± 2 <sup>a</sup>
Positive end-expiratory pressure	CMV	5 ± 0.0	5 ± 0.0	5 ± 0.0	5 ± 0.0	5 ± 0.0	5 ± 0.4	6 ± 0.40	6 ± 0.4	7 ± 0.5	6 ± 0.5	6 ± 0.5	6 ± 0.6
	APRV	5 ± 0.0	5 ± 0.0	5 ± 0.0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Fio <sub>2</sub>	CMV	0.21 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.5 ± 0.1	0.6 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	0.9 ± 0.1
	APRV	0.21 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	0.5 ± 0.1	0.5 ± 0.1	0.6 ± 0.1 <sup>a</sup>	0.8 ± 0.1 <sup>a</sup>	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
Time low	CMV	n/a	0.62 ± 0.08	0.65 ± 0.05	0.68 ± 0.05	0.62 ± 0.05	0.61 ± 0.05	0.69 ± 0.07	0.74 ± 0.10	0.70 ± 0.10	0.74 ± 0.10	0.74 ± 0.10	0.66 ± 0.10
	APRV	n/a	0.62 ± 0.08	0.65 ± 0.05	0.68 ± 0.05	0.62 ± 0.05	0.61 ± 0.05	0.69 ± 0.07	0.74 ± 0.10	0.70 ± 0.10	0.74 ± 0.10	0.74 ± 0.10	0.66 ± 0.10

CMV, conventional mechanical ventilation; APRV, airway pressure release ventilation; n/a, not applicable.

<sup>a</sup>indicates  $p < .05$  determined by two-way analysis of variance with repeated measures.

Ventilatory data recorded at baseline and respective time points of the experiment. All values are means ± SEM.



**Figure 5.** Lung histology. Histologic appearance of bronchi after mechanical ventilation with either airway pressure release ventilation (APRV) or conventional mechanical ventilation (CMV) following smoke inhalation injury (hematoxylin and eosin, original magnification  $\times 200$ ). A, Control group, CMV. There is multifocal loss of cilia. B, APRV group and C, CMV. There is diffuse loss of cilia, with degeneration and necrosis of the epithelium. Note multifocal ulceration of epithelium with variable amounts of fibrin, hemorrhage, and cellular debris. Histologic appearance of alveolar walls, mechanical ventilation following smoke inhalation injury (hematoxylin and eosin, original magnification  $\times 400$ ). D, CMV controls, stretching and disruption of alveoli. E, APRV and F, CMV. Multifocal alveolar septae are moderately thickened with, type 2 pneumocyte hyperplasia, and multifocal intra-alveolar fibrin, edema, and inflammatory cells, consisting predominantly of neutrophils and macrophages. Alveolar septae are variably lined by mats of fibrin and cellular debris (hyaline membranes).

mortality. Nevertheless, survival was similar in both groups.

Early smoke inhalation injury varies significantly from other causes of ARDS, and these differences likely have a significant influence on the efficacy of various interventions (31). Hypoxemia in early ARDS induced by systemic inflammation or sepsis results from alveolar edema and intrapulmonary shunt (32). In early

smoke inhalation injury, small airway damage and obstruction predominate, bronchial blood flow increases, and increased blood flow to poorly ventilated lung segments results in ventilation-perfusion mismatch (23, 33). Airway resistance is further increased by bronchospasm and mucus production. These changes are heterogeneous throughout the lungs, producing varying time con-

stants among pulmonary segments (34). These unique pathologic features of early inhalation injury have important clinical implications, as increased airway resistance in addition to decreased lung compliance can complicate patient-ventilator interactions.

Use of APRV in patients with increased airway resistance is not well reported outside of case reports in severe asthma (35). General recommendations include prolonging the time low segment of the ventilator cycle to maintain peak expiratory flow rate termination at around 50% (20). However, the flow-time waveform represents a summation of all lung segments. In a heterogeneous injury, this strategy may not guarantee that adequate ventilation will occur or that alveolar collapse will not occur in all segments. Early smoke inhalation injury is also characterized by alveolar instability from surfactant deactivation and alveolar edema (9–10). High Paws are often required to maintain adequate oxygenation. As an “open-lung” strategy in APRV, Paw, alveolar pressure, and peak airway pressure are nearly equivalent. Since smoke inhalation causes a heterogeneous injury, many different zones of pulmonary compliance may exist. Some small lung segments may be viable (36) and subject to barotrauma during APRV, while others may be fully collapsed and unlikely to be affected by any ventilator strategy (37).

The threshold for a “safe” Pplat during ventilation is unclear. *Post hoc* analysis of the ARDS Network trial of low TV ven-

Table 4. Histology scoring

Group	Left Apical			Left Caudal			Right Apical			Right Caudal			Cumulative		
	Bronchi	Alveolar Wall	Hem and Edema	Bronchi	Alveolar Wall	Hem and Edema	Bronchi	Alveolar Wall	Hem and Edema	Bronchi	Alveolar Wall	Hem and Edema	Bronchi	Alveolar Wall	Hem and Edema
Airway pressure release ventilation	3.7 ± 0.2 <sup>a</sup>	2.9 ± 0.3	3.0 ± 0.3	3.6 ± 0.3 <sup>a</sup>	3.0 ± 0.4	2.6 ± 0.5	3.6 ± 0.3 <sup>a</sup>	3.1 ± 0.3	3.0 ± 0.4	3.4 ± 0.4 <sup>a</sup>	3.0 ± 0.3	3.5 ± 0.4 <sup>a</sup>	13.3 ± 0.8 <sup>a</sup>	11.6 ± 1.1	11.6 ± 1.0
Conventional mechanical ventilation	3.3 ± 0.3 <sup>b</sup>	2.5 ± 0.3	2.6 ± 0.4	3.9 ± 0.1 <sup>b</sup>	2.4 ± 0.2	3.4 ± 0.3	3.4 ± 0.3 <sup>b</sup>	2.8 ± 0.3	2.9 ± 0.4	3.7 ± 0.2 <sup>b</sup>	2.5 ± 0.2	2.3 ± 0.4	13.9 ± 0.8 <sup>b</sup>	10.2 ± 0.5	11.2 ± 0.7
Control	0.0 ± 0.0	1.8 ± 0.2	1.2 ± 0.4	0.0 ± 0.0	2.2 ± 0.2	2.2 ± 0.5	0.2 ± 0.2	2.0 ± 0.3	1.5 ± 0.3	0.2 ± 0.2	2.0 ± 0.4	1.3 ± 0.3	0.3 ± 0.2	8.2 ± 0.9	6.4 ± 1.4

Hem, hemorrhage; Apical, sections of the lungs taken from the apex; basal, sections of the lungs taken from the basal areas of the lower lobes. Cumulative scores include a sum of all four side- and location-specific scores.

<sup>a</sup> $p \leq .05$  for airway pressure release ventilation vs. control; <sup>b</sup> $p \leq .05$  for conventional mechanical ventilation vs. control, by Kruskal-Wallis test and post hoc Wilcoxon Two-Sample test, with Bonferroni correction for multiple comparisons.

All values are means ± SEM.

tilation observed that mortality paralleled Pplat, even at values lower than 20 cm H<sub>2</sub>O (38). Although the peak inspiratory pressure and Pplat seen with APRV and CMV were similar in our study, APRV required a higher Paw to maintain oxygenation. This observation has been documented previously (26, 29). While high TV and peak inspiratory pressure are commonly associated with ventilator-induced lung injury, some authors suggest that a high Paw also contributes to ventilator-induced lung injury (37, 39). Furthermore, in cases of increased expiratory resistance, Paw may underestimate mean alveolar pressure (39). The combination of increased airway resistance in smoke inhalation injury and short expiratory times with APRV may cause conditions in which mean alveolar pressure exceeds Paw, potentiating the deleterious effects of mechanical ventilation.

PFR was lower in APRV at 24 hrs, but by 48 hrs it was similar in both groups. This similarity may be related to stabilization of the airway injury and the process of cast formation in our model. Indeed, we observed a decrease in casts on bronchoscopy beginning at the 24-hr time point. By 48 hrs, the pathophysiology may be more similar to other causes of ARDS.

Postmortem histology scores were indistinguishable between the APRV and CMV groups, substantiating our observation that, in this model, neither method is superior to the other. Both CMV and APRV animals showed higher bronchial injury scores, which is a consistent finding in smoke inhalation injury (30). In addition, not only APRV and CMV animals, but also control animals, demonstrated alveolar inflammation and hemorrhage/edema, indicating the potential for ventilator-induced lung injury even in

lungs not subjected to smoke. Histologic analysis also demonstrated the well-known heterogeneity of ARDS. We observed high variability in the sections examined, particularly with respect to the degree of alveolar inflammation and alveolar hemorrhage/edema present in the field of view, with lobules of relatively normal alveoli adjacent to lobules of alveoli undergoing extensive degeneration and inflammation.

Methodological factors likely affected the results of our study. The initial 10 mL/kg TV settings employed in both groups during the first 2 hrs after injury were designed to effect rapid carbon monoxide clearance. Clinically relevant comparison of APRV to CMV started at 2 hrs after injury. We chose to use a pressure-targeted approach since we were comparing CMV to a type of pressure-controlled ventilation. As ARDS ensued and subsequent increases in Paw occurred, we began lowering TV to maintain a Pplat of <35 cm H<sub>2</sub>O. We allowed Pplat to exceed 35 cm H<sub>2</sub>O only if the animals were refractory to other interventions, such as decreasing the TV to 4 mL/kg in the CMV group or manipulating the time low in the APRV group. Pplat exceeded 35 cm H<sub>2</sub>O in five pigs in the APRV group and three pigs in the CMV group. This perhaps could have been avoided if we had accepted lower pH and PO<sub>2</sub> criteria in our algorithm, such as those used in the ARDS Network (pH <7.15 and PO<sub>2</sub> of 55 mm Hg). Some experts recommend volume-cycled ventilation at 6 mL/kg even in the absence of lung injury (40, 41). It is unknown whether rapid institution of a low-TV strategy would have slowed the progression of ARDS or improved survival in this severe model.

It was difficult to maintain spontaneous breathing in this model. While most pigs in the APRV group had some degree of spontaneous breathing, it was not consistent due to requirements to keep the pigs deeply sedated and pain free. The total sedation requirements were similar in each group. Proponents of APRV suggest the benefits of APRV are diminished in the absence of spontaneous breathing (42). However, the improvement in oxygenation seen with spontaneous breathing is not immediate and often occurs after 24 hrs (28). Because most patients with smoke inhalation injury often have coexisting cutaneous burns and/or trauma, they often require significant amounts of sedation and analgesia to facilitate wound care or other invasive procedures. APRV may not be superior to CMV during this initial phase of treatment, in which sedation and analgesia may interfere with spontaneous breathing. Other factors, such as disconnection from mechanical ventilation during bronchoscopy, may also lead to lung derecruitment during this phase of care.

Our model involved severe inhalation injury without cutaneous burns, whereas a combination of both injuries, with a lesser degree of inhalation injury, is more common. Previous animal models have documented a synergistic effect from the combination of inhalation and cutaneous injury as compared to inhalation injury alone. It is also known that the response to a given injury can vary among subjects. The 48-hr duration of this study prevents us from reporting on which mode of ventilation may be beneficial in the longer-term management of smoke inhalation injury. Also, because we excluded three APRV animals that clearly



did not respond as expected to smoke inhalation and did not develop evidence of significant injury, our study did not follow an “intention-to-treat” design.

We did not use adjuvant therapies, such as inhaled bronchodilators, heparin, or N-acetylcysteine, which are commonly used in clinical practice. Inline suctioning and scheduled fiberoptic bronchoscopy were vital in ensuring survival in our study, but may have also led to derecruitment during pulmonary toilet and suctioning.

## CONCLUSIONS

Despite its use for nearly 2 decades, there is a paucity of data comparing APRV to CMV in the management of ARDS. Furthermore, there are no studies evaluating APRV for early management of smoke inhalation injury. This injury is a unique pathophysiologic process characterized predominantly by a small airway lesion, and its initial management should be differentiated from that of other causes of ARDS. In this model, when compared to CMV with a target Pplat of 35 cm H<sub>2</sub>O, APRV was associated with a lower PFR at 12, 18, and 24 hrs after injury, despite a higher Paw from 6 hrs after injury until the end of the study. Thus in this experiment, APRV appeared not to be of benefit when compared to CMV in management of ARDS in the first 48 hrs. However, these observations should be balanced by the fact that spontaneous breathing was not a consistent feature of this model. Further investigations on the use of APRV in smoke inhalation injury are warranted to characterize its role in the longer-term management of patients with smoke-induced ARDS.

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